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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/020,746	02/09/98	ASHKENAZI A	P1101P1

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EXAMINER	
KAUFMAN, L	

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 09/29/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/020,746	ASHKENAZI, ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *01 July 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,13 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9 and 10* is/are allowed.

6)☒ Claim(s) *1-8,12,13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6, 7,11*
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

The amendments filed July 1, 1999 has been entered.

Election/Restrictions

Applicant's election of Group I in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

The IDS submitted August, 1998 has been considered to the extent possible. Several of the references said to be submitted in parent application 08/857,216 were neither present nor considered in that case: 91,102, 105, 114, 115, 119, 161, 166, 173, 191, 201 and 265.

Drawings

Figure 1 of the instant application is presented on two separate panels. 37 C.F.R. § 1.84 (u)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. The two sheets must be identified by the same number followed by a capital letter. The two sheets of drawing which are labeled "Figure 1" in the instant specification should be renumbered "Figures 1A and 1B". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u)(1), Applicant is required to change the Brief Description of the Drawings and the rest of the specification accordingly. Figures with multiple panels should be referred to as, for example, "Figures 5A-5C" or the equivalent instead of "Figure 5".

Specification

Applicants are advised that the ATCC has moved from Rockville, MD to Manassas, VA, effective March 23, 1998. The correct address is now:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

The specification should be amended (p. 69, line 5) to reflect the correct address for the ATCC.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12, 13, and 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A) an antibody which specifically binds an Apo-2 polypeptide that consists of the amino acid sequence of SEQ ID NO:1 or B) an antibody that binds the same epitope as the antibody produced by the hybridoma ATCC HB-12456 or C) a hybridoma cell line producing the antibody of either A or B, does not reasonably provide enablement for 1) an antibody that binds an Apo-2 polypeptide which is not identical to SEQ ID NO:1 or 2) an antibody which specifically binds Apo-2 but which does not bind the same epitope as that from hybridoma ATCC HB-12456 and which is an agonist and/or blocking antibody or 3) a hybridoma cell line producing either the antibody of 1 or 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of

direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to an antibody that binds Apo-2 or a hybridoma producing that antibody. The prior art does not teach an Apo-2 polypeptide. It does teach related polypeptides Apo-3/DR3 (Marsters et al., 1996, #190 cited by Applicants) and DR4 (Pan et al., 1997, #220 cited by Applicants). Also taught is an antibody to Apo-3 (Marsters et al., *ibid.*, see p. 1675, 5th paragraph), but that antibody would not be expected to bind Apo-2 as the disclosed sequence of Apo-2 and Apo-3 share only about 24% identity overall and 34% identity in the death domain. Therefore, the prior art does not teach an antibody that would reasonably be expected to bind Apo-2. It is acknowledged that the skill in the art is high as it relates to the discovery of TNF receptor family proteins, of which Apo-2 is a member, but not as it relates to predicting sequences of the receptor proteins or, as a result, the necessary structure of an antibody that would bind an unknown member of the receptor family. It was known at the time the invention was made that the ligand for Apo-2 (called Apo-2L or TRIAL) is involved in causing apoptotic cell death (p. 2, lines 26-31 or the specification).

The term Apo-2 as defined in the specification includes naturally occurring and variant polypeptides (p. 11, line 20 to p. 12, line 14). According to the specification (p. 12, lines 8-18), a variant must be a biologically active Apo-2 and have at least 80% amino acid sequence identity with SEQ ID NO:1. "Biologically active" is broadly defined as the ability to modulate (stimulate or inhibit) apoptosis (page 15, lines 32-36). Neither the specification nor the prior art has taught a naturally occurring or other variant that can inhibit apoptosis. Because of the low sequence identity of SEQ ID NO:1 to known related receptors, it is not predictable what other sequences an Apo-2 polypeptide could have while still being "biologically active" and distinguishable from other receptors of the TNF receptor family. The only Apo-2 polypeptides disclosed has SEQ ID NO:1, and no other naturally occurring or variant receptors are disclosed.

While the specification discloses (p. 66, lines 5-14) that 8/22 antibody supernatants from cells obtained from animals immunized with the extracellular domain of SEQ ID NO:1 were positive for binding to Apo-2, only a single antibody was show to be either blocking or agonistic

(Examples 10 and 11). Making an antibody that is agonistic or blocks the activity of the protein to which it binds is unpredictable and complex even if the regions of activity in the protein are known, which is not the case here. The blocking activating described for antibody 3F11.39.7 in the instant application suggest that the antibody is binding to a site (epitope) which is different from the site to which Apo-L binds, suggesting competitive binding with the ligand. Also that antibody binding site is a site which can lead to activation of Apo-2. Finding other sites which allow an binding antibody to have either agonistic or blocking activity or both in the absence of structural information about the receptor besides its amino acid sequence and general domain structure would require undue experimentation without a reasonable expectation of success since so little is known about which amino acids or potential epitopes would be likely to be necessary for receptor activity. Therefore, making an antibody that does not bind the same epitope as 3F11.39.7, yet which is agonistic and/or blocking would likewise require undue experimentation.

Because of the unpredictability, breadth of the claims due to the variation in Apo-2 sequence permitted, lack of teachings in the specification and prior art about how the structure of the receptor is related to its activity, and, for claims 3 and 4, the unpredictability of making an antibody other than one that binds the same epitope of 3F11.39.7 but which had a agonistic or blocking activity, it would require undue experimentation to make the antibody and producing-hybridoma as they are currently broadly claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7, 12, 13, 15-18 and dependent claims 2-6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 15-18 are indefinite because it is unclear what the metes and bounds of "Apo-2" are. The specification says that this term includes variants (p. 11, second ¶), and

variants are about 80% identical to SEQ ID NO:1 and are agonistic or antagonistic modulators of apoptosis (third paragraph of p. 15). Because it is not clear what 80% identical means since there is no defined way of calculating identity and because the activity is represented by two opposite functions, what structures are encompassed by the claims is not clear.

Claim 1 is indefinite because it is not clear what "specifically binds" means. It is unclear is this term is intended to imply that the antibody binds only Apo-2 and no other protein type or if it can cross-react with other related receptors such as DR4, as is the case for disclosed antibody 3F11.39.7 (p. 47, line 34).

Claim 7 is indefinite because it is unclear what "the biological characteristics" are and which characteristics the claimed antibody must have. The specification does not provide a limiting definition (p. 21, lines 6-10). It is unclear if this means the claimed antibody must have all biological characteristics, including structure and function, in which case it would have to be identical to the antibody produced by the hybridoma of ATCC HB-12093 and this claim would have the same breadth as claim 7, or if only some of the characteristics, *e.g.*, certain structural or functional aspects, are meant. Because of this ambiguity, the metes and bounds of the claim are not clear.

Claims 12, 13, 15 and 16 are indefinite because a composition must comprise more than one component. It is unclear what the composition includes besides an Apo-2 antibody, and it is unclear if the Apo-2 antibody is an active ingredient of the composition or merely present in trace amounts. Knowing whether the Apo-2 antibody is critical to the composition is necessary to understand the breadth of the claim. If the antibody is the active ingredient, this rejection could be obviated by adding to the end of the claim another component (*e.g.*, a buffer or diluent) which is generally accepted in the art not to be an active ingredient.

cmk
9/27/99

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Wiley et al. (A, US Patent 5,763,223) describe the cytokine TRAIL, also known as Apo-2 ligand, to which trail binding proteins like Apo-2 can bind.

The prior art of record does not teach an Apo-2 antibody as claimed. Nor is an antibody to DR4 taught, which is pertinent since disclosed antibody 3F11.39.7 binds DR4 as well as Apo-2 (p. 47, line 34).

Term Usage

It is noted that the art also refers to Apo-2 as DR5 and TRAIL-2.

Conclusion

Claims 9 and 10 are allowed.

Claim 8 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Claire M. Kaufman

Patent Examiner, Art Unit 1646

September 27, 1999